REMARKS

This is in response to the Office Action of December 29, 2009. The features of claims 65 and 66 are incorporated into claim 22, and claims 65 and 66 are accordingly cancelled, without prejudice. Claim 64 is amended in view of the foregoing amendment of claim 22. New claim 69 recites the chondroitin sulfate and dextran sulfate embodiments of the invention formerly recited in oral medicine claim 22. The features of claims 62 and 68 are incorporated into claim 41, and claims 62 and 68 are accordingly cancelled, without prejudice. Claim 67 is amended in view of the foregoing amendment of claim 41. New claim 70 recites the chondroitin sulfate and dextran sulfate embodiments of the invention formerly recited in manufacturing method claim 41. No new matter has been added by way of the present claim amendments. Claims 22, 41, 64, 67, 69, and 70 are now pending in the application.

Rejections under 35 U.S.C. § 103(a)

Claims 22, 41, 62, 65, 66, and 68 were rejected under 35 U.S.C. § 103(a) as being unpatentable over US 5,013,557 to Tai (hereinafter "Tai") in view of US 5,464,612 to Matoba et al. (hereinafter "Matoba") and further in view of "The Rationale for E2020 as a Potent Acetylcholinesterase Inhibitor" by Kawakami et al. (hereinafter "Kawakami"). Office Action, pages 2-4. Claims 64 and 67 were rejected as being unpatentable over Tai in view of Matoba, Kawakami, and JP 4-346937 to Morikazu et al. (hereinafter "JP '937"). Office Action, pages 4-5. Applicants respectfully traverse the foregoing rejections.

THE INVENTION. The present invention provides an oral medicament which avoids unpleasant taste. The presently claimed medicament comprises a mixture which includes a medicine – donepezil hydrochloride – known to be characterized by unpleasant taste, and an acidic polysaccharide – specifically, carrageenan (claims 22, 41, 64, 67) or chondroitin sulfate or dextran sulfate (claims 69 and 70). In the present invention, the mixture is in a homogeneous blend and said basic medicine and acidic polysaccharide are in intimate contact and undergo an electric interaction. Specifically, there is an ionic interaction between donepezil hydrochloride, which is positively charged, and the specified acidic polysaccharide, which is negatively

charged. Together, they form a water-insoluble ionic complex. This prevents the unpleasant tasting donepezil medicine from dissolving in saliva.

TAI MAKES MICROCAPSULES. Tai is concerned with taste-masking by way of spray-dried microcapsules of sucralfate and a polymer. As taught, for instance, in column 7, lines 65 – column 8, line 10, the Tai taste masking composition comprises: (A) a microcapsule core comprising ... (a) sucralfate ... and (b) a polymer soluble in the gastric fluids ...; and (B) over the core ... (a) a bulking agent ...; and (b) a lubricating agent." Thus, Tai coats his medicine with a polymer to avoid contact of the medicine with the taste buds in the mouth. Tai then dissolves the polymer (via gastric juices) to make the medicine available to the body.

In contrast, the present invention provides "a homogeneous blend [in which donepezil hydrochloride] and acidic polysaccharide are in intimate contact in order to form an electric interaction and to prevent the basic medicine from dissolving in saliva." Applicants' homogeneous blend is neither taught nor suggested by Tai. Instead, Tai teaches away from a homogeneous blend, and requires the use of coated particles.

TAI USES A DIFFERENT TYPE OF MEDICINE. Tai fails to show other requisite features of the instantly claimed invention, as well. This is due to a misunderstanding of the term "basic" medicine in the context of the present invention. The Examiner's implication in the Office Action that sucralfate is a basic medicine is inaccurate. Sucralfate is also generically known as "basic aluminum sucrose sulfate" and is an aluminum salt of an acidic medicine (sucrose sulfate). Sucralfate is a basic aluminum sucrose sulfate having a negative charge, and therefore does not form a complex by an ionic interaction as is formed in the claimed invention. In Tai, the mechanism for masking a bitter taste of sucralfate involves an aluminum component (of a salt of sucralfate) and alginic acid being blended together. Upon administration, moisture from water or from the oral cavity is taken in. The bitter substance (sucralfate) is present in the gel state, and the area of contact with the specific region of the tongue (which tastes the bitterness) is reduced. As a result, the bitterness is reduced, but this mechanism is completely different from the masking effects of the presently claimed invention.

Since sucralfate is a negatively-charged compound, it cannot form a complex by ionic interaction with a specified acidic polysaccharide, which is negatively charged, as is required by

the claimed invention. Thus, Tai does not teach a medicine which is similar to donepezil hydrochloride.

SHOTGUN DISCLOSURE. Moreover, for the other main component of Applicants' invention, Tai teaches in column 6 that "The polymers soluble in the gastric fluids useful in the present invention are those polymers which will bind to sucralfate to form spray dried spheroidal microcapsule ... and will dissolve in the gastric fluids to permit sucralfate to form a cytoprotective gel. ... Suitable polymers soluble in the gastric fluids in the present invention may be selected from the group consisting of maltodextrins, gelatin, acacia, agar, alginic acid, carrageenan, guar, pectin, tragacanth, xanthan, carboxymethyl cellulose, methyl cellulose, microcrystalline cellulose, polyacrylic acid, polyvinyl alcohol, polyvinyl pyrrolidone polymers, and the like, and mixtures thereof. ... In a most preferred embodiment, the polymer soluble in the gastric fluids is maltodextrin." This constitutes a "shotgun disclosure." There is no motivation to select carrageenan from the extensive listing set forth in the Tai reference.

Applicants respectfully submit that the rejection of record, which requires abandoning Tai's medicine, sucralfate, for a very different type of medicine, donepezil hydrochloride, and then selecting carrageenan instead of one of the many other medicines listed by Tai (e.g., why not maltodextrin?) is imbued with impermissible hindsight based upon Applicants' disclosure. What other factor would motivate a person of ordinary skill in the art to make the choices that are necessary to change the Tai disclosure into Applicants' invention? Applicants respectfully remind the Examiner that the fact that a claimed product is within the broad field of the prior art, and one might arrive at that product by selecting specific items and conditions, does not render the product obvious in the absence of some directions or reasons for making such selection. *Ex parte Kuhn*, 132 USPQ 359 (POBA 1961). Similarly, a compound within the scope of a generic formula which encompasses a large number of compounds cannot render a product obvious absent some direction or reasons for selecting the substituents required to arrive at the compound. *In re Baird*, 29 USPQ2d 1550, 16 F.2d 380 (Fed. Cir. 1994).

COMBINATION NOT MOTIVATED. Neither Kawakami nor Matoba nor Morikazu cure the deficiencies of Tai. Kawakami gives no description of the unpleasant taste of E2020 to the patient and thus the Examiner is using Kawakami only for disclosing donepezil

hydrochloride. The Kawakami disclosure provides no motivation or rationale for combining Kawakami with the other references. The Examiner turns to Matoba to demonstrate that it was known in the art, at the time of the present invention, that basic drugs have a bitter taste and that the taste may be masked with a coating composition. However, the proposed combination of Tai, Kawakami, and Matoba (and Morikazu) is based entirely on the Examiner's improper hindsight reasoning. As far as the record shows, the present inventors were the first to discover the bitter taste of donepezil hydrochloride. Thus, those of ordinary skill at the time of the present invention would not have looked to Matoba, as presently suggested by the Examiner, because there was no recognition of the problem of bitterness with respect to donepezil.

APPLICANTS DISCOVERED THE PROBLEM. The discovery of a problem is inventive, even if once discovered, the solution is obvious. *In re Antonson*, 124 USPQ 132 (CCPA 1959). In the Amendment filed September 16, 2008, Applicants submitted Evidence A-D to support that the unpleasant, basic taste of donepezil hydrochloride was not known at the time the present application was filed. See pages 10-12 thereof. The Examiner has responded by pointing to *KSR*, which held that the combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results. *KSR Int'l Co. v Teleflex Inc.*, 127 S. Ct. 1727 (2007). Although the Examiner may be correct regarding the holding of *KSR*, that holding does not address whether the discovery of a new problem is obvious. Applicants note that the Examiner has failed to address the substance of the evidence provided in the last response (i.e., their showing that one of ordinary skill in the art was not aware of the bitter or unpleasant taste of donepezil hydrochloride before the priority dates of the present application).

CONCLUSION. Thus, for at least the reasons discussed above, the presently claimed invention is not rendered *prima facie* obvious by the cited prior art references. Reconsideration and withdrawal of both of the outstanding rejections is respectfully requested.

Obviousness-Type Double Patenting Rejection

Claims 22, 41, 62, and 64-68 stand rejected on the ground of obviousness-type double

patenting as being unpatentable over claims 1, 3, 6, and 12 of US 6,576,677 to Ukai et al. (hereinafter "Ukai") in view of Tai. Office Action, pages 6-7. Applicants respectfully traverse.

Applicants respectfully submit that the presently claimed invention is patentably distinct from the Ukai in view of Tai, among other reasons because the mechanism by which the present invention prevents the bitter taste of donepezil hydrochloride is different than that of Ukai in view of Tai. The mechanism of preventing a bitter taste of donepezil hydrochloride in the claimed invention is as follows: the ionic interaction between donepezil hydrochloride (positively-charged) and the specified acidic polysaccharide, such as carrageenan (negatively-charged) results in the formation of a water-insoluble ionic complex. In this way, a strong masking advantage of preventing a bitter taste is obtained, due to the inhibition of elution of donepezil hydrochloride being a basic medicament into water or saliva.

In contrast, Ukai discloses a mixture of donepezil hydrochloride (positively-charged) and polyvinyl pyrrolidone ("PVP") to form a water-soluble chelate by the following mechanism to prevent bitter taste: PVP forms a water-soluble chelate (not insoluble) and the molecular weight thereof is increased. The effect of preventing bitter taste is due to inhibition of tongue cells in the oral cavity that sense bitter taste due to the increased molecular weight of the formed chelate. The pyrrolidone group of PVP has an oxygen "–O–" which traps donepezil hydrochloride (positively-charged) as a chelate such as pyrrolidone–O–donepezil hydrochloride–O–pyrrolidone.

Thus, it is apparent from the above descriptions that the presently claimed invention is patentably distinct from Ukai, even in view of Tai. Accordingly, reconsideration and withdrawal of the double patenting rejection is respectfully requested.

Claims 69 and 70

It is respectfully submitted that claims 69 and 70 distinguish over the prior art and over the Ukai patent for all of the reasons discussed above, and additionally because they require that the "acidic polysaccharide is at least one member selected from the group consisting of chondroitin sulfate, dextran sulfate, and salts thereof," which moieties are neither taught nor

suggested by the prior art herein.

CONCLUSION

In view of the foregoing, Applicants believe the pending application is in condition for allowance. A Notice of Allowance is earnestly solicited.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Richard Gallagher, Reg. No. 28,781, at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.147; particularly, extension of time fees.

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Respectfully submitted,

By_____

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